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Short Communication

Long-term persistence of symptoms of dyspnoea in COVID-19 patients

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To the Editor

Even after recovering from the acute phase of COVID-19, patients may report the persistence of symptoms that have become known as 'long COVID' (Akbarialiabad *et al.*, 2021). In one meta-analysis of nine studies conducted on 1,816 patients between three weeks and three months after discharge from hospital, the persistence of dyspnoea, chest pain and a cough affected 37%, 16% and 14% of patients, respectively (Cares-Marambio *et al.*, 2021). These proportions gradually decrease with follow-up time. In a cross-sectional study conducted on 574 patients eight months after recovery, dyspnoea was the most frequent sequelae affecting 29% of patients (Zheng *et al.*, 2021). In one prospective cohort study conducted on 588 COVID-19 patients, 14% of patients reported dyspnoea at eight months of follow-up (Soraas *et al.*, 2021). In this study, we aim to estimate the rate of persistent dyspnoea in French COVID-19 patients, as evaluated after at least six months of follow-up and to investigate the risk factors for this persistence.

We identified confirmed COVID-19 patients who reported dyspnoea during the acute phase of the disease from among a cohort of 3,737 patients tested at our institute between 3 March and 27 April 2020 (Lagier *et al.*, 2020). Patients with pre-existing chronic respiratory diseases and chronic heart disease were excluded from this analysis. Information on demographics, comorbidities, and acute symptoms were retrieved from medical files.

The selected patients were interviewed by telephone and asked to complete a questionnaire on possible persistent dyspnoea. Statistical analysis was performed by R 3.6.1 software (R Core team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2020. URL: http://www.r-project.org). Multiple logistic regression model were applied to explore the association between patient characteristics and dyspnoea at the acute phase and at the follow-up time. Variables with p-values < 0.2 in the univariable analysis were included in the multivariable analysis. Of the 3,737 COVID-19 patients, 3,222 had no known chronic respiratory disease and/or chronic heart disease at the time of inclusion and 880/3,222 (27.3%) reported dyspnoea at the acute phase of COVID-19. Being female or obese and consulting six or more days after the onset of symptoms were independently associated with dyspnoea. Patients with dyspnoea at admission were more likely to receive oxygen therapy. In univariate analysis, hypoxaemia, oxygen saturation $\leq$94%, C-reactive protein $>$5 mg/L, neutrophils $>$7.5 Giga/L, eosinophils $<$0.1 Giga/L, lymphocyte $<$1 Giga/L associated with dyspnoea, but a multivariate analysis was not conducted due to a high proportion of missing information. (Table 1). Of 880 patients, we randomly selected 838 patients for the telephone interview. Among them, 496/838 (59.2%) answered the questionnaire and 342/838 (40.8%) were lost to follow-up. Patients who responded were significantly less likely to report hypertension, to present severe symptoms, to require oxygen upon inclusion, to undergo prolonged hospitalisation and

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Table 1
Risk factors for dyspnoea during the acute phase (n=3,222)

		No dyspnoea (n=2,342)%	Dyspnoea (n=880)%	Univariate analysis OR [95%CI] p-value	Multivariate analysis** OR [95%CI] p-value
Age	Mean ± SD	43.6 ± 15.8	43.7 ± 15.5		
	Range	18–96	18–94		
	< 45 (n=1,720)	1,255 (53.6)	465 (52.8)	ref	
	≥ 45 (n=1,502)	1,087 (46.4)	415 (47.2)	1.03 [0.88–1.21] 0.71	
Sex	Male (n=1,464)	1,107 (47.3)	357 (40.6)	ref	ref
	Females (n=1,758)	1,235 (52.7)	523 (59.4)	1.31 [1.12–1.54] **0.0007**	1.38 [1.17–1.61] **0.0001**
Chronic conditions					
Hypertension	No (n=2,845)	2,080 (88.8)	765 (86.9)	ref	
	Yes (n=377)	262 (11.2)	115 (13.1)	1.19 [0.94–1.52] **0.14**	
Diabetes	No (n=2999)	2179 (93.0)	820 (93.2)	ref	
	Yes (n=223)	163 (7.0)	60 (6.8)	0.98 [0.71–1.34] 0.89	
Cancer	No (n=3,138)	2,280 (97.4)	858 (97.5)	ref	
	Yes (n=84)	62 (2.6)	22 (2.5)	0.94 [0.55–1.56] 0.81	
Obesity	No (n=2,882)	2,124 (90.7)	758 (86.1)	ref	ref
	Yes (n=340)	218 (9.3)	122 (13.9)	1.57 [1.23–1.99] **0.0002**	1.45 [1.13–1.84] **0.003**
Co-medications					
Beta blockers	No (n=3,141)	2,285 (97.6)	856 (97.3)	ref	ref
	Yes (n=81)	57 (2.4)	24 (2.7)	1.12 [0.66–1.85] 0.63	
Dihydropyridine	No (n=3,117)	2,269 (96.9)	848 (96.4)	ref	
	Yes(n=105)	73 (3.1)	32 (3.6)	1.17 [0.74–1.82] 0.46	
Angiotensin-converting enzyme inhibitors	No (n=3,197)	2,325 (99.3)	872 (99.1)	ref	
	Yes (n=25)	17 (0.7)	8 (0.9)	1.25 [0.47–3.08] 0.59	
Angiotensin II receptor blocker	No (n=3,107)	2,258 (96.4)	849 (96.5)	ref	
	Yes (n=115)	84 (3.6)	31 (3.5)	0.98 [0.62–1.51] 0.93	
Metformin	No (n=3,125)	2,273 (97.1)	852 (96.8)	ref	
	Yes (n=97)	69 (2.9)	28 (3.2)	1.08 [0.67-1.72] 0.72	
Fenofibrate	No (n=3,203)	2,329 (99.4)	874 (99.3)	ref	
	Yes (n=19)	13 (0.6)	6 (0.7)	1.23 [0.38–3.48] 0.68	
Statin	No (n=3,154)	2,290 (97.8)	864 (98.2)	ref	
	Yes (n=68)	52 (2.2)	16 (1.8)	0.82 [0.43–1.46] 0.48	

(*continued on next page*)

Table 1 (*continued*)

		No dyspnoea (n=2,342)%	Dyspnoea (n=880)%	Univariate analysis OR [95%CI] p-value	Multivariate analysis** OR [95%CI] p-value
COVID-19 status at inclusion					
Time between onset of COVID symptoms and admission	< 6 days(n=1,599)	1,239 (52.9)	360 (40.9)	ref	ref
	≥ 6 days (n=1,623)	1,103 (47.1)	520 (52.1)	1.62 [1.38–1.90] **<0.0001**	1.51 [1.28–1.77] **<0.0001**
NEWS Score 2	Low (n=3,017)	2,216 (94.6)	801 (91.0)	ref	
	Medium (n=125)	89 (3.8)	36 (4.1)	1.12 [0.75–1.66] 0.58	
	High (n=80)	37 (1.6)	43 (4.9)	3.22 [2.06–5.03] **<0.0001**	
Oxygen	No (n=3,034)	2,256 (96.3)	778 (88.4)	ref	
	Yes (n=188)	86 (3.7)	102 (11.6)	3.44 [2.52–4.69] **<0.0001**	3.13 [2.31–4.25] **<0.0001**
Oxygen saturation (SpO2) %*	>94% (n=2,754)	1,968 (96.1)	786 (92.4)	ref	
	≤ 94% (n=145)	80 (3.9)	65 (7.6)	2.03 [1.43–2.89] **<0.0001**	
Chest Computed Tomography*					
	Normal (n=509)	370 (32.2)	139 (26.8)	ref	
	Limit (n=756)	542 (47.1)	214 (41.3))	1.05 [0.82-1.35] 0.69	
	Intermediate (n=329)	203 (17.7)	216 (24.3)	1.65 [1.23-2.22] 0.001	
	Severe (n=74)	35 (3.0)	39 (7.6))	2.97 [1.81-4.87] <0.01	
C-reactive protein *	≤ 5mg/L (n=1,466)	1,093 (63.2)	373 (56.1)	ref	
	>5mg/L(n=929)	637 (36.8)	292 (43.9)	1.34 [1.12-1.62] **0.001**	
Neutrophils*	≤ 7.5 Giga/L (n=2,604)	1,894 (97.8)	710 (96.5)	ref	
	>7.5 Giga/L (n=68)	42 (2.2)	26 (3.5)	1.65 [0.96-2.78] **0.046**	
Eosinophils*	≥0.1 Giga/L (n=684)	520 (26.9)	164 (22.3)	ref	
	<0.1 Giga/L (n=1,988)	1,416 (73.1)	572 (77.7)	1.28 [1.04-1.58] **0.015**	
Lymphocytes*	≥ 1 Giga/L (n=2,370)	1,731 (89.4)	639 (86.8)	ref	
	< 1 Giga/L (n=302)	205 (10.6)	97 (13.2)	1.28 [0.98-1.67] 0.06	
D-Dimer*	≤ 0.5 μg/ml (n=335)	227 (58.7)	108 (57.8)	ref	
	>0.5μg/ml (n=239)	160 (41.3)	79 (42.3)	1.04 [0.72-1.50] 0.84	
Fibrinogen*	≤ 4g/L (n=290)	216 (46.2)	74 (35.2)	ref	
	>4 g/L (n=388)	252 (53.8)	136 (64.8)	1.58 [1.11-2.24] 0.008	
PCR Ct value < 16 at admission *	No (n=2,460)	1,773 (93.3)	687 (94.9)	ref	
	Yes (n=164)	127 (6.7)	37 (5.1)	0.75 [0.50–1.11] **0.14**	

NEW Score 2: National Early Warning Score
*Oxygen saturation, Chest Computed Tomography, C-reactive protein, neutrophil, eosinophil, lymphocyte, D-Dimer, Fibrinogen and Ct <16 were not included in the multivariate due to >5% missing data
**only significant results are presented in the multivariate analysis

Table 2
Risk factors for dyspnoea at follow-up (n=469)

		No dyspnoea persistence (n=373)%	Dyspnoea persistence (n=123)%	Univariate analysis OR [95%CI] p-value	Multivariate analysis** OR [95%CI] p-value
Age	Mean ± SD	41.0 ±13.4	43.6 ± 12.8		
	Range	18–89	20–72		
	< 45 (n=285)	226 (60.6)	59 (48.0)	ref	
	≥ 45 (n=211)	147 (39.4)	64 (52)	1.67 (1.08–2.57) **0.01**	1.74 [1.15–2.63] **0.009**
Sex	Male (n=176)	138 (37.0)	38 (30.9)	ref	
	Females (n=320)	235 (63.0)	85 (69.1)	1.31 [0.83–2.09] 0.22	
Chronic conditions					
Hypertension	No (n=451)	343 (92.0)	108 (87.8)	ref	
	Yes (n=45)	30 (8.0)	15 (12.2)	1.59 [0.76–3.18] **0.16**	
Diabetes	No (n=471)	353 (94.6)	118 (95.9)	ref	
	Yes (n=25)	20 (5.4)	5 (4.1)	0.75 [0.21–2.11] 0.57	
Cancer	No (n=483)	362 (97.1)	121 (98.4)	ref	
	Yes (n=13)	11 (2.9)	2 (1.6)	0.54 [0.06–2.55] 0.43	
Obesity	No (n=431)	327 (87.7)	104 (84.6)	ref	
	Yes (n=65)	46 (12.3)	19 (15.5)	1.29 [0.69–2.38] 0.37	
Co-medications					
Beta blockers	No (n=486)	367 (98.4)	119 (96.8)	ref	ref
	Yes (n=10)	6 (1.6)	4 (3.3)	2.05 [0.42–8.82] 0.26	
Dihydropyridine	No (n=487)	365 (97.9)	122 (99.2)	ref	
	Yes(n=9)	8 (2.1)	1 (0.8)	0.37 [0.008–2.84] 0.34	
Angiotensin-converting enzyme inhibitors	No (n=493)	372 (99.7)	121 (98.4)	ref	
	Yes (n=3)	1 (0.3)	2 (1.6)	6.15 [0.31–363.66] **0.09**	
Angiotensin II receptor blocker	No (n=484)	364 (97.6)	120 (97.6)	ref	
	Yes (n=12)	9 (2.4)	3 (2.4)	1.01 [0.17–4.14] 0.99	
Metformin	No (n=487)	366 (98.1)	121 (98.4)	ref	
	Yes (n=9)	7 (1.9)	2 (1.6)	0.86 [0.09–4.62] 0.86	
Fenofibrate	No (n=493)	371 (99.5)	122 (99.2)	ref	
	Yes (n=3)	2 (0.5)	1 (0.8)	1.52 [0.03–29.42] 0.73	
COVID-19 status at inclusion					
Time between onset of COVID symptoms and admission	< 6 days(n=207)	146 (39.1)	61 (49.6)	ref	ref
	≥ 6 days (n=289)	227 (60.9)	62 (50.4)	0.65 [0.42–1.01] **0.04**	0.65 [0.43–0.99] **0.045**

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Table 2 (*continued*)

		No dyspnoea persistence (n=373)%	Dyspnoea persistence (n=123)%	Univariate analysis OR [95%CI] p-value	Multivariate analysis** OR [95%CI] p-value
NEWS Score 2	Low (n=473)	357 (95.7)	116 (94.3)	ref	
	Medium (n=13)	9 (2.4)	4 (3.3)	1.37 [0.41–4.52] 0.61	
	High (n=10)	7 (1.9)	3 (2.4)	1.32 [0.33–5.18] 0.69	
Oxygen	No (n=467)	353 (94.6)	114 (92.7)	ref	
	Yes (n=29)	20 (5.4)	9 (7.3)	1.39 [0.54–3.31] 0.42	
Saturation oxygen (SpO2) %	> 94% (n=453)	335 (93.3)	118 (97.5)	ref	
	≤94% (n=27)	24 (6.7)	3 (2.5)	0.35 [0.07–1.20] 0.08	
Chest Computed Tomography*	Normal (n=74)	55 (29.9)	19 (27.9)	ref	
	Limit (n=105)	77 (41.9)	28 (41.2)	1.05 [0.53-2.07] 0.88	
	Intermediate (n=58)	40 (21.7)	18 (26.5)	1.30 [0.61-2.79] 0.50	
	Severe (n=15)	12 (6.5)	3 (4.4)	0.72 [0.18-2.84] 0.64	
C-reactive protein*	≤ 5mg/L (n=219)	162 (60.0)	57 (62.6)	ref	
	>5mg/L (n=142)	108 (40.0)	34 (37.4)	0.89 [0.53-1.50] 0.66	
Neutrophil*	≤ 7.5 Giga/L (n=407)	300 (97.1)	107 (100.0)	ref	
	>7.5 Giga/L (n=9)	9 (2.9)	0 (0.0)	0.00 [0.00-1.21] 0.07	
Eosinophil*	≥0.1 Giga/L (n=96)	82 (26.5)	14 (13.1)	ref	
	<0.1 Giga/L (n=320)	227 (73.5)	93 (86.9)	2.40 [1.27-4.81] **0.004**	
Lymphocyte*	≥ 1 Giga/L (n=376)	281 (90.0)	95 (88.8)	ref	
	< 1 Giga/L (n=40)	28 (9.1)	12 (11.2)	1.27 [0.56-1.69] 0.51	
D-Dimer*	≤ 0.5 μg/ml (n=71)	51 (73.9)	20 (60.6)	ref	
	>0.5μg/ml (n=31)	18 (26.1)	13 (39.4)	1.84 [0.69-4.84] 0.17	
Fibrinogen*	≤ 4g/L (n=36)	28 (40.6)	8 (30.8)	ref	
	>4 g/L (n=59)	41 (59.4)	18 (69.2)	1.54 [0.54-4.66] 0.38	
PCR Ct value < 16 at admission *	No (n=396)	297 (93.7)	99 (95.2)	ref	
	Yes (n=25)	20 (6.3)	5 (4.8)	0.75 [0.21–2.13] 0.57	
Viral shedding ≥ 10 days*	No (n=285)	220 (89.8)	65 (83.3)	ref	
	Yes (n=38)	25 (10.2)	13 (11.7)	1.76 [0.78–3.81] 0.12	
Hospitalisation ≥ 10 days	No (n=485)	366 (98.1)	119 (97.6)	ref	
	Yes (n=10)	7 (1.9)	3 (2.5)	1.32 [0.22–5.88] 0.69	

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Table 2 (*continued*)

		No dyspnoea persistence (n=373)%	Dyspnoea persistence (n=123)%	Univariate analysis OR [95%CI] p-value	Multivariate analysis** OR [95%CI] p-value
Transfer to the ICU	No (n=485)	364 (97.6)	121 (98.4)	ref	
	Yes (n=11)	9 (2.4)	2 (1.6)	0.69 [0.07-3.29] 0.61	
Hydroxychloroquine + azithromycin ≥ 3 days	No (n= 46)	35 (9.4)	11 (8.9)	ref	
	Yes (n= 450)	338 (90.6)	112 (01.1)	1.05 [0.50–2.38] 0.88	

NEW Score 2: National Early Warning Score

*Chest Computed Tomography, C-reactive protein, neutrophil, eosinophil, lymphocytes, D-Dimer, Fibrinogen, Ct < 16 and viral shedding were not included in the multivariate due to >5% missing data

**only significant results are presented in the multivariate analysis

had lower rates of mortality, as compared with all patients reporting dyspnoea at inclusion (Supplementary Table 1)

Among these 496 patients, 123 (24.8%) reported persistent dyspnoea. The duration between the onset of symptoms and the interview was 44.0 ± 10.3 weeks, ranging from 31.6 to 63.1 weeks. Being aged ≥ 45 years old and consulting early during the acute phase (less than six days after the onset of symptoms) were independently associated with persistent dyspnoea (Table 2).

Lung damage in COVID-19 patients could be explained by various underlying mechanisms, including viral and immune-mediated implications (Liu *et al.*, 2020), which could cause the persistence of dyspnoea. Dyspnoea is, by nature, a highly subjective experience. Women are more prone to suffer dyspnoea, possibly due to a decreased surface area for pulmonary gas exchange relative to lung size-matched men (Cory *et al.*, 2015). People who are obese have a decreased functional residual capacity and expiration reserve volume (Parameswaran *et al.*, 2006). Therefore, it is not surprising that female and obese COVID-19 patients had a higher risk for dyspnoea at admission. We observed that dyspnoea was more frequent in patients consulting more than six days after the onset of symptoms, suggesting that it takes a few days for the virus to provoke such symptoms. The association with a high viral load upon admission suggests a direct cytopathic effect of viruses on lung tissue.

The association of symptom persistence with being older may suggest a lower capacity of cell regeneration due to ageing. We have no hypothesis, however, to explain why early consultation was associated with the persistence of dyspnoea.

The use of the telephone interview has some limitations, including the lack of respiratory functional tests to quantify dyspnoea levels and a lack of information about smoking status. In addition, patients lost to follow-up could potentially include a high proportion of patients who fully recovered their respiratory function. Despites these limitations, our study underlined the high prevalence of the persistence of dyspnoea (24.8%) in COVID-19 patients and its association with older age. Further investigation with a clinical evaluation of respiratory function over time is required in these patients.

Ethical approval

This study was approved by the Comité de Protection des Personnes Nord Ouest II (No. 2021-A01183-33) on 22/07/2021.

Consent for publication

All authors gave their consent for publication.

Availability of data and materials

All the data for this study will be made available upon reasonable request to the corresponding author.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Philippe Gautret and Didier Raoult devised the project, the main conceptual ideas. Nhu Ngoc Nguyen, Jean Christophe Lagier, Matthieu Million, Thi Loi Dao, Line Meddeb collected the data. Van Tuan Hoang and Nhu Ngoc Nguyen analyzed and interpreted data. Nhu Ngoc Nguyen and Philippe Gautret wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2021.11.035.

References

Akbarialiabad H, Taghrir MH, Abdollahi A, Ghahramani N, Kumar M, Paydar S, et al. Long COVID: a comprehensive systematic scoping review. Infection 2021.

Cares-Marambio K, Montenegro-Jimenez Y, Torres-Castro R, Vera-Uribe R, Torralba Y, Alsina-Restoy X, et al. Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. Chron Respir Dis 2021;18 14799731211002240.

Cory JM, Schaeffer MR, Wilkie SS, Ramsook AH, Puyat JH, Arbour B, et al. Sex differences in the intensity and qualitative dimensions of exertional dyspnea in physically active young adults. J Appl Physiol (1985) 2015;119:998–1006.

Lagier JC, Million M, Gautret P, Colson P, Cortaredona S, Giraud-Gatineau A, et al. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: a retrospective analysis. Travel Med Infect Dis 2020;36:101791.

Liu J, Zheng X, Tong Q, Li W, Wang B, Sutter K, et al. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. J Med Virol 2020;92:491–4.

Parameswaran K, Todd DC, Soth M. Altered respiratory physiology in obesity. Can Respir J 2006.

Soraas A, Bo R, Kalleberg KT, Ellingjord-Dale M, Landrø NI . Self-reported memory problems eight months after non-hospitalized COVID-19 in a large Cohort. medRxiv 2021.

Zheng D, Zhang L, Feng B, Liu Y, Liu H, Hu J, et al. Long-term clinical sequelae and immunological features of COVID-19 survivors: a cross-sectional study in Wuhan. China. Lancet (preprint) 2021.